UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/608,890	06/30/2000	Gary L. Johnson	CPI-004DVCP3CN	1962

959 7590 11/22/2005

LAHIVE & COCKFIELD, LLP.
28 STATE STREET
BOSTON, MA 02109

EXAMINER	
BASI, NIRMAL SINGH	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 11/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/608,890	JOHNSON, GARY L.	
	Examiner	Art Unit	
	Nirmal S. Basi	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2005*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-62 and 65* is/are pending in the application.

4a) Of the above claim(s) *59-62 and 65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Amendment filed 8/1/05 has been entered. Applicant's arguments filed 11/18/04 have been considered and are addressed below. CRF filed 4/7/05 has been entered.

2. In the amendment filed 8/1/05 Applicant amended claim 60 to directly depend on 59. Applicant requests that claims 59 and 60 be rejoined in light of the amendment. Claims 59 and 60 remain joined because said claims were never separated. Claims 59-64 remain withdrawn from further consideration as being drawn to methods requiring nucleic acid, said methods reading on gene therapy. The invention of claims 53-58, methods of using the polypeptide of SEQ ID NO: 2 and 4, do not require gene therapy and can be practiced by agents regulating MEKK protein activity. The requirement is still deemed proper and is therefore made FINAL.

Objections

The disclosure is objected to because of the following informalities:

3. The specification remains objected to because Applicants are required to use the heading "Brief Description of the Drawings" to describe the drawings. See MPEP 608.01(f). On page 8, Applicant has written Brief Description Of The Figures"

Appropriate correction is required.

4. Applicant provided a sequence listing on 1/25/01 but did not direct its entry into the specification. There was no amendment stating that the prior sequence listing be cancelled and replaced with the sequence listing dated 1/2/501. A further sequence listing was provided on 11/18/04. Again there was no amendment stating that the prior sequence listing be cancelled and replaced with the sequence listing dated 11/18/04. The record is not clear as which sequence listings should be cancelled. Appropriate correction is required.

Claim Rejections - 35 USC 112, Second Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 53-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 53 is indefinite because it is not clear what activity of the MEKK protein is regulated in the cell such that apoptosis of the cell is regulated, so as to allow the metes and bounds of the claim cannot be determined. It is suggested, to overcome the rejection, a specific activity be disclosed. Further it is not clear if "directly regulates" means the agent must bind to the MEKK to exert its effect or if regulation is by some other means. Applicant argues Claim 53 has been amended to indicate that the agent modulates the activity of an MEKK 1 polypeptide in a cell such that apoptosis of the cell is regulated. Applicant argues

that the specification clearly teaches that expression of MEKK 1 polypeptides in a cell induces apoptosis. Applicant also argues is not required to elucidate the exact mechanism by which apoptosis occurs in order to satisfy the conditions of patentability. Applicant's arguments have been fully considered but are not found persuasive. It is still not clear what activity of the MEKK protein is regulated in the cell such that apoptosis of the cell is regulated. The claim requires that a specific activity of the MEKK 1 be modulated. Even though the expression of the MEKK 1 in a cell causes apoptosis it is a result of the modulation of the "activity". Arguing that apoptosis occurs as consequence of the modulation of an undisclosed activity does not define the "activity" itself. The question is what activity of MEKK 1 is modulated that results in regulation of apoptosis of the cell. The specific activity modulated will determine if cell apoptosis is increased or decreased. Applicant has not addressed Examiners arguments as they pertain to if "directly regulates" means the agent must bind to the MEKK to exert its effect or if regulation is by some other means.

Claims 54 and 55 remain indefinite because it is not clear what activity of the kinase domain of MEKK protein is regulated, so as to allow the metes and bounds of the claim cannot be determined. Further, it is not clear which fragment of MEKK contains the critical structural feature of the invention to be classified as the kinase domain of MEKK protein. Also, it is not clear which fragment of MEKK contains the critical structural feature of the invention to be classified as the regulatory domain of MEKK protein. Although, the proteins of SEQ ID NOs 2 and 4 contain regions of the kinase domain and regulatory

domain of MEKK protein, it is not clear at what amino acid said domains start and end, so as to allow the metes and bounds of the claim to be determined. It is suggested, to overcome the rejection, kinase domain and regulatory domain be identified by using SEQ ID NO: and specific amino acid positions in said SEQ ID NO: to indicate the start and end of said domains.

Claim 56 remains indefinite because it is not clear which fragment of MEKK contains the critical structural feature of the invention to classified as the kinase catalytic domain of MEKK protein. Although the proteins of SEQ ID NOs 2 and 4 contain regions of the kinase catalytic domain of MEKK protein it is not clear at what amino acid said domain starts and end, so as to allow the metes and bounds of the claim cannot be determined. It is suggested, to overcome the rejection, kinase catalytic domain be identified by using SEQ ID NO: and specific amino acid positions in said SEQ ID NO: used to indicate the start and end of said domain.

Applicant argues the specification teaches the exact location of the kinase and regulatory domains of representative MEKK 1 molecules, e.g., MEKK 1.1 and MEKK1.2 set forth at SEQ ID N0s:2 and 4. Applicant argues that the kinase domain is located between residues 409 and 672 of MEKK 1.1 and between residues 1331 and 1594 of MEKK 1.2. The regulatory domain is located between residues 1 and 408 of MEKKI.I and between residues 1 and 1328 of MEKKI.2. Applicant argues the activity of a kinase domain is well known to one of skill in the art. Applicant argues the specific activities and targets of the kinase domain of MEKK are disclosed. For example, the specification teaches at page 16, lines

9-13, that the MEKK molecules of the invention interact with, and directly phosphorylate members of the MAP kinase kinase family (MEKS or MKKs), MEKI, MEKZ, MKKI, MKKZ, or the stress-activated kinases (SEKs), and the Jun kinase kinases. Also argued, page 49, lines 24-27 of the specification teach that that MEKK 1 is capable of bindjng to Ras and that the binding occurs via the COOH kinase domain. Applicant's arguments have been fully considered but are not found persuasive. Providing an example of an activity does define all the activities encompassed by the claim so as to allow the metes and bounds of the claim to be determined. Further the exact location of the kinase domain and the regulatory domain are not disclosed. The kinase domain being located between residues 409 and 672 of MEKK 1.1 and between residues 1331 and 1594 of MEKK 1.2, and the regulatory domain being located between residues 1 and 408 of MEKKI.I and between residues 1 and 1328 of MEKKI .2 only provides a general area where the domains are located. For example just saying a person lives between Washington DC and New York City does not provide his/her exact address. The postman will not be able to deliver a letter addressed to MR. MEKK 1 living between Washington DC and New York City. In analogy such is the case in instant claims. The disclosure of the kinase and regulatory domains being located between the disclosed residues does not define the domains themselves. If the kinase domain is residues 409 and 672 of MEKK 1.1 and residues 1331 and 1594 of MEKK 1.2 it must be indicated as such. If the regulatory domain is residues 1 and 408 of MEKKI.I and residues 1 and 1328 of MEKKI.2 it must be indicated as such. Also just by indication a domain does not

necessarily mean the activity of the domain is automatically known. For example the kinase domain may contain a ligand binding domain, a number of different catalytic domains or even another regulatory domain. Therefore the claims require the recitation of a specific activity and specific domains to overcome the rejection.

Claims 57 and 58 are rejected for depending upon an indefinite base (or intermediate) claim.

Claim Rejections - 35 USC 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 53-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for regulating cell apoptosis of a cell containing an MEKK-1 polypeptide set forth in SEQ ID NO:2 or MEKK1.2 polypeptide set forth in SEQ ID NO:4 comprising contacting the cell with an agent that binds to MEKK protein of SEQ ID NO:2 or 4 or the truncated MEKK disclosed in Example 15, wherein said agent regulate the ability of said MEKK to be phosphorylated or to phosphorylate a substrate such as MAP kinase or other substrate disclosed in the Examples such that apoptosis of the cell is regulated, does not reasonably provide enablement for other MEKKs or agents that stimulate MEKK activity. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant argues the claims have been amended such that they are limited to MEKK 1 molecules, i.e., polypeptides of SEQ ID NOs:2 and 4. Applicant argues the specification provides multiple working examples of molecules that stimulate MEKK activity and further provide a number of assays that one of skill in the art would use to screen molecules for the ability to stimulate MEKK molecules. Applicant further argues the, also provided, are assays that one of skill in the art would use to test for the ability of an agent to stimulate MEKK molecules. Applicant states, "based on the teachings and working examples set forth in the specification, the ordinary skilled artisan would be able to make and use the claimed invention using only routine experimentation. Applicant's arguments have been fully considered but are not found persuasive. It must be noted that the claims as written do not even require the agent to interact with the MEKK 1 protein to regulate apoptosis of the cell. What the claims require is that the agent directly modulate the activity an MEKK1. The activity of the MEKK1 may be the ability to phosphorylate a particular protein. The particular protein could get phosphorylated by another compound, which does not necessarily have to be MEKK1. Therefore the claims are limited to the ability to regulate an undisclosed activity, which does not necessarily require the presence of MEKK1. The specification has disclosed agents that interact (bind) to the MEKK1 and then regulate apoptosis by a specific manner.

The specification discloses MEKK of SEQ ID NOs: 2 and 4 encoded by the nucleic acid of SEQ ID NOs: 1 and 3 respectively. Specification also discloses cell death resulting from MEKK expression required the kinase activity of the enzyme, page 101. The MEKK contains an NH2-terminal regulatory domain that serves to regulate a second structural domain comprising a COOH-terminal protein kinase catalytic domain that is capable of phosphorylating an MKK protein, page 21. Although the specific fragment of MEKK1 that constitutes catalytic domain is not disclosed, the specification states the "preferred catalytic domain truncated MEKK" contains residues from about 409 to about 672 of SEQ ID NO:2 and about 1331 to about 1584 of SEQ ID NO:4, page 30. Further, the specific fragment of MEKK1 that constitutes the regulatory domain is not disclosed, the specifcation states the "preferred regulatory domain truncated MEKK" contains residues from about 1 to about 408 of SEQ ID NO:2 and about 1 to about 1328 of SEQ ID NO:4, page 30. Specifcation also discloses cell death resulting from MEKK expression required the kinase activity of the enzyme, page 101. Figure 11 and Example 15 show MAP kinase activity was increased in cells expressing deletions of amino acids 211-215 of SEQ ID NO:2.

The ability to phosphorylate substrate is contained in the kinase catalytic domain of the protein of SEQ ID NO:2 and 4. The specific start and end of said domain is not disclosed. Further a protein comprising only residues of 409 to 672 of SEQ ID NO:2 and 1331 to 1584 of SEQ ID NO:4 has not been disclosed to regulate cell apotosis. There is no disclosure showing that a complete lack of the regulatory domain will produce a functional protein. Although, the ability of

regulatory region of MEKK to regulate the phosphoryaltion activity of the catalytic domain has been shown to be affected by a specific mutation in this regulatory region, other parts of the molecule are most likely needed to stabilize the catalytic domain for functionality. Further, the specifcation discloses no mutations in the catalytic domain that may produce functional protein. The claimed method can only be practiced if the catalytic domain has functional kinase activity, i.e. capable of phosphorylation. Proteins with 85% identity to SEQ ID NO:2 and 4, with mutations in the catalytic domain have not been shown to be functional. The specifcation nor prior art disclose any mutations that that may be produced in the catalytic domain of MEKK1 so as to produce a functional polypeptide capable of MAP kinase phosphorylation or phosphorylation of some other substrate that results in apoptosis of the cell. Therefore, while the skilled artisan, in light of the specification, would be able to use the MEKK1 disclosed in SEQ ID NO:2 and 4, or the polypeptide disclosed in Example 15, to regulate the MEKK protein to be phosphorylated or phosphorylate a substrate to regulate cell apoptosis, there is no disclosure in the specification or prior art that variants encompassed by only the name MEKK (name provides no structure and function association), variants with 85% identity with the regulatory domain of SEQ ID NO:2 or 4, variants with 85% identity with catalytic kinase domain of SEQ ID NO:2 or 4, or proteins that can be used to regulate activity of a MEKK protein in a cell such that apoptosis of cell is regulated. Also, it must be noted that no agents are disclosed that increase apoptosis of cells by increasing MEKK activity. Therefore applicants are not enabled for methods involving the use of agents to

increase apoptosis by regulating MEKK activity. The scope of the claims, which encompass MEKK polypeptide variants without disclosure of a specific catalytic structure disclosed in SEQ ID NO:2 or 4 which is capable of functioning as a kinase, said MEKK having the ability to be phosphorylated or to phosphorylate MAP kinase or other substrate disclosed in the Examples, are not enabled by the disclosure. The disclosure does not teach how to make or identify such variants, or to use a commensurate number of the variants, which did not share all the catalytic properties encompassed by the peptide of SERQ ID NO:2 or 4. Due to the large quantity of experimentation necessary to identify/make the polypeptides used in instant method, the lack of direction/guidance presented in the specification regarding the mutation, production, identification and characterization of said polypeptides, the unpredictability of the effects of mutation on the structure and function of proteins (since mutations of SEQ ID NO:2 and 4 are also encompassed by the claim), and the breadth of the claim which fail to recite the structural critical feature of the invention required for activity, undue experimentation would be required of the skilled artisan to make or use the claimed invention in its full scope.

For all the above reasons, the disclosure is insufficient to teach one of skill in the art how to use the invention. A review of *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) clearly points out the factors to be considered in determining whether a disclosure would require undue experimentation and include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of

the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. All of these factors are considerations when determining the whether undue experimentation would be required to use the claimed invention. As is evidence in the discussions *supra*, each of these factors has been carefully considered in the instant grounds of rejection, and it is maintained that undue experimentation would be required by the skilled artisan to use the instant invention.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

A Claims 53, 54 rejected under 35 U.S.C. 102(b) as being anticipated by Dubroff (US Patent 5,080,647).

Dubroff discloses a method for regulating apoptosis of a cell comprising contacting the cell with an agent that directly regulates the that apoptosis of the cell. Dubroff discloses compositions and methods of their use in killing undifferentiated epithelial cells (see abstract, claims and columns 1-6). The compositions and method of Dubroff will inherently modulate the activity of an MEKK 1 polypeptide set forth as SEO ID NO:2 or 4 (phosphorylation or cell death for example) because the compounds disclosed will cause cell apoptosis and degradation or denaturation of the proteins contained within. Therefore the disclosure of Dubroff meets the limitations of claims 53 and 54, absent evidence to the contrary.

B Claims 53, 54, 57 and 58 rejected under 35 U.S.C. 102(e) as being anticipated by Naficy (US Patent 5,419,759).

Naficy discloses a method for regulating apoptosis of a cell comprising contacting the cell with an agent that directly regulates the that apoptosis of the cell. Naficy discloses compositions and methods of their use in killing HIV infected cells (see abstract, columns 1-14). In column 9, Naficy discloses killing H-9 lymphocytes with the use of ether. The compositions and method of Naficy will inherently modulate the activity of an MEKK 1 polypeptide set forth as SEO ID NO:2 or 4 (phosphorylation or cell death for example) because the compounds disclosed will cause cell apoptosis and degradation or denaturation of the proteins contained within. The method of Naficy is used to kill T cells, which are involved in an inflammatory response. Therefore the disclosure of Naficy meets the limitations of claims 53-54 and 57-58, absent evidence to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nirmal S. Basi
Art Unit 1646
October 17, 2005

JOSEPH MURPHY
PATENT EXAMINER